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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,538	LI ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

2. In view of the Supplemental Appeal Brief filed on 5-06-2005, PROSECUTION IS HEREBY REOPENED. New grounds of rejection set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Petition under Rule 37 CFR § 1.48(a)

3. A Petition to Correct inventorship under Rule 37 CFR § 1.48(a) was filed on 9-20-2004, however it did not include an oath or declaration by the actual inventors as required by Rule § 1.63 and Rule § 1.48(a)(3). However, the Supplemental Rule 37 CFR § 1.48(a) Petition filed 9-30-04 provided the required oath or declaration, the Petition is now considered complete, and is therefore entered.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3, and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

The instant claims are drawn to "[A]n oligonucleotide having a nucleotide sequence of from 15 to about 26 nucleotides and having one or more phosphorothioate internucleoside linkage, that inhibits one or more specific histone deacetylase isoforms, but less than all histone deacetylase isoforms, wherein the oligonucleotide is complementary to a region of RNA or double-stranded DNA that encodes a portion of HDAC-1 (SEQ ID NO: 2)."

The breadth of the claimed invention encompasses those oligonucleotides which possess a specific function, namely those that inhibit one or more specific histone deacetylase isoforms, but less than all histone deacetylase isoforms. However, the specification as filed does not provide a clear nexus between the structure of the claimed oligonucleotides and the specifically defined function recited in these claims. According to the claims the structures of these oligonucleotides are from 15 to about 26 nucleotides in length, having one or more phosphorothioate internucleoside linkages, wherein the oligonucleotide is **complementary** to ***a***

region of RNA or double-stranded DNA that encodes ***a portion*** **of HDAC-1** (SEQ ID NO: 2). To the extent that the instant claims nor the specification as filed provides a precise definition for the terms "complementary," "a region" or "a portion of," the scope of the claimed invention encompasses, for example, "a region," may encompass a 5 nucleobase region, wherein the oligonucleotide is "complementary" to a 5 nucleobase "portion" of HDAC-1 (SEQ ID NO: 2).

According to the specification as filed at page 19, 2nd paragraph, "[F]or purposes of the invention, the term "complementary" means having the ability to hybridize to a genomic region, a gene, or an RNA transcript thereof under physiological conditions. Such hybridization is ordinarily the result of base-specific hydrogen bonding between complementary strands, preferably to form Watson-Crick or Hoogsteen base pairs, although other modes of hydrogen bonding, as well as base stacking can lead to hybridization. As a practical matter, such hybridization can be inferred from the observation of specific gene expression inhibition, which may be at the level of transcription or translation (or both)."

Therefore, the scope of the instant claims encompass those oligonucleotides that hybridize to a portion (of undefined length) of HDAC-1 (SEQ ID NO: 2), by means of undefined modes of hydrogen bonding that are not the result of art recognized Watson-Crick or Hoogsteen hydrogen bonding.

The specification as filed at page 23, Table 1, provides the structures of several human isotype specific oligonucleotides and their mismatch oligonucleotides, and Figure 10A describe the effect of HDAC isotype-specific antisense oligonucleotides on HDAC isotype protein expression in human A549 cells. However, the structures of these oligonucleotides cannot be used to predict the full scope of antisense oligonucleotides encompassed by the instant claims.

For example, the mismatch control oligonucleotide HDAC-1 MM effectively inhibits the expression of HDAC-2, HDAC-3, and HDAC-4, however HDAC-1 was not very effective against HDAC-1. The mismatch control is complementary (i.e. hydrogen bonds via Watson Crick base pairing) to nucleotides 1594-1598 of HDAC-1 SEQ ID NO: 2, and functions to inhibit one or more specific histone deacetylase isoforms, but less than all histone deacetylase isoforms. The observation that even the mismatch control oligonucleotide HDAC-1 MM meets all the limitations of the instant claims provides further evidence that the breadth of the claimed invention is extremely broad.

Moreover, the specification as filed describes the sequences of HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8, and provides methods for determining the ability of a putative oligonucleotide to inhibit one or more specific histone deacetylase isoforms, but less than all of the histone deacetylase isoforms according to HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8. However, a generic search of term "histone deacetylase," in GenBank resulted in 263 hits for genes encoding a histone deacetylase. This search demonstrates that there is an extremely large number of nucleic acid sequences encoding histone deacetylase isoforms, that were not adequately described in the specification as filed. Therefore, it is unclear how Applicants were in possession of the full scope of oligonucleotides which function to inhibit one or more specific deacetylase isoforms, but less than all of the histone deacetylase isoforms, when all of the isoforms of histone deacetylase were not know as of the earliest effective filing date of the current application.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written

Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

See MPEP § 2163, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

Additionally, "[T]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required." See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483.

The compounds according to the present invention, described in Table 1 of the specification as filed which are complementary to a region of RNA or double-stranded DNA that

encodes a portion of HDAC-1 (SEQ ID NO: 2), and inhibits one or more, but less than all histone deacetylase isoforms can not be used to predict the structures of oligonucleotides that are encompassed by the instant claims, since the structures of inhibitory oligonucleotide compounds can only be identified empirically. According to Branch (1998), "RNAs are complex molecules with intricate internal structures...[r]ecent studies emphasize the extent to which native RNA structure restricts the binding of ODNs *[oligonucleotides]*....[t]hey found that 'surprisingly few' ODNs bound stably to the mRNA, and concluded that binding is probably 'confined to those regions in the RNA which provide an accessible substructure.'" (page 49, col. 1, paragraphs 2-3). Additionally, Branch (1998) state that "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found ***empirically*** by screening a large number of candidates for their ability to act inside cells." (page 49, col. 1, paragraph 3)

Although Applicants provide a means for testing the ability of a putative oligonucleotide to inhibit one or more deacetylase isoforms according to HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8, there is no guidance provided in the specification as filed or in the prior art searched that would have allowed the skilled artisan to predict the structures oligonucleotides according to the present invention that inhibit the expression of one or more HDAC isoforms, but not all of the 263 forms of histone deacetylase genes that are currently known in the art. Apart from further experimentation, the skilled artisan would not have been able to predict the structures of the full scope of the claimed oligonucleotides encompassed by the instant invention. According to MPEP § 2163, providing a method for isolating the claimed invention is not evidence of description.

Moreover, claim 1 recites that the claimed oligonucleotides are "15 to about 26" nucleotides in length. However the specification as filed does not provide support for this limitation. The specification discloses the nucleotide range of "about 15 to about 26." Claim 1 was amended 2-14-03, wherein applicants deleted the limitation "about 13 to 35" and replaced it with "15 to about 26." However, there is no support for removing the limitation "about" from the phrase "about 15 to about 26," as recited on page 22, 3rd paragraph of the instant specification. This amendment to the claims is considered new matter by the examiner. As per MPEP 714.02, Applicants should show support for amended claims.

6. Claims 1-3 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making oligonucleotides that are complementary to the extent that the oligonucleotides hybridize to HDAC-1 (SEQ ID NO: 1) by means of Watson-Crick or Hoogsteen base pairing, and wherein the oligonucleotide inhibits the expression of one or more histone deacetylase genes, but not all of HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC–5, HDAC–6, HDAC –7, HDAC-8, does not reasonably provide enablement for making oligonucleotides which are complementary to a portion of HDAC-1 by Applicant's definition, wherein hybridization occurs by some other means of hydrogen bonding other than Watson-Crick or Hoogsteen base pairing, wherein said oligonucleotide inhibits the expression of one or more histone deacetylase genes, but not all of HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC–5, HDAC–6, HDAC –7, HDAC-8, or the 263 HDAC genes described in GenBank. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed Cir. 1988).

The instant claims are drawn to "[A]n oligonucleotide having a nucleotide sequence of from 15 to about 26 nucleotides and having one or more phosphorothioate internucleoside linkage, that inhibits one or more specific histone deacetylase isoforms, but less than all histone deacetylase isoforms, wherein the oligonucleotide is complementary to a region of RNA or double-stranded DNA that encodes a portion of HDAC-1 (SEQ ID NO: 2)."

According to the specification as filed at page 19, 2nd paragraph, "[F]or purposes of the invention, the term "complementary" means having the ability to hybridize to a genomic region, a gene, or an RNA transcript thereof under physiological conditions. Such hybridization is ordinarily the result of base-specific hydrogen bonding between complementary strands, preferably to form Watson-Crick or Hoogsteen base pairs, although other modes of hydrogen bonding, as well as base stacking can lead to hybridization. As a practical matter, such hybridization can be inferred from the observation of specific gene expression inhibition, which may be at the level of transcription or translation (or both)."

Therefore, the scope of the instant claims encompass those oligonucleotides that hybridize to a portion (of undefined length) of HDAC-1 (SEQ ID NO: 2), by means of undefined modes of hydrogen bonding that are not the result of art recognized Watson-Crick or Hoogsteen hydrogen bonding. Furthermore, the scope of the claims encompasses oligonucleotides that

inhibit one or more histone deacetylase isoforms, but not all histone deacetylase isoforms. The specification as filed describes how to assay for the ability of a putative oligonucleotide to inhibit eight isoforms of HDAC, however there is evidence that there are at least 263 different forms of histone deacetylase.

To the extent that Applicants have not provided sufficient guidance, instruction, and or description of the other modes of hybridization encompassed by the term "complementary" as defined by Applicants in the specification as filed (see above), Applicants are not enabled to make the full scope of oligonucleotides encompassed by the instant claims.

The skilled artisan would have to resort to de novo experimentation in order to identify the various modes of hybridization involving other means of hydrogen bonding between the oligonucleotides of the instant invention and a region of RNA or double stranded DNA that encodes a portion of HDAC-1, wherein said oligonucleotide inhibits one or more histone deacetylase isoforms, but not all histone deacetylase isoforms. Moreover, as stated above there are at least 263 different forms of histone deacetylase. Therefore, as significant amount of experimentation would have to be undertaken to ascertain the ability of a putative oligonucleotide to inhibit one or more histone deacetylase isoforms, but not all isoforms.

In regards to the level of unpredictability in the antisense oligonucleotide art, Branch (1998) stated, "RNAs are complex molecules with intricate internal structures...[r]ecent studies emphasize the extent to which native RNA structure restricts the binding of ODNs *[oligonucleotides]*....[t]hey found that 'surprisingly few' ODNs bound stably to the mRNA, and concluded that binding is probably 'confined to those regions in the RNA which provide an accessible substructure.'" (page 49, col. 1, paragraphs 2-3). Additionally, Branch (1998) state

that "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found ***empirically*** by screening a large number of candidates for their ability to act inside cells." (page 49, col. 1, paragraph 3)

In addition to identifying other means of hydrogen bonding besides Watson-Crick and Hoogsteen base pairing, the skilled artisan would further have to identify functional oligonucleotides which inhibit one or more of the at least 263 various forms of histone deacetylase, but not all forms of histone deacetylase.

Therefore, it is concluded that the skilled artisan would have to resort to undue experimentation in order to practice the full scope of the claimed invention. This conclusion is based upon the breadth of the claimed invention, the lack of guidance in the specification as filed in regards to identifying oligonucleotides which hybridize by other than Watson-Crick or Hoogsteen base pairing, and furthermore identifying the ability of these oligonucleotides to specifically inhibit one or more HDAC isoforms, but not all forms of HDAC.

Claim Rejections - 35 USC § 103

7. Claims 1-3 and 5 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al. (IDS reference A3, IDS filed 10/09/01) in view of the collection of Taylor et al. (DDT VOI. 4, No. 12, 12/12/99, pages 562-567), Bennett et al. (Chapter 2, pages 13-46, from Methods in Molecular Medicine: Antisense Therapeutics, 1996), Page 5, Baracchini et al. (U.S. Patent 5,801,154) and Cowsert (U.S. Patent 5,951,455) and the sequence of HDAC-1 (instant SEQ ID NO: 2 from GenBank Accession No. U50079, Applicants own admission, page 9 of specification) for the same reasons of record set forth in the prior Official actions.

8. Applicant's arguments filed 5-06-2005 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the combination of Yoshida and others fails to render the claimed invention obvious because there is no motivation or suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Applicants further traverse on the grounds: (1) the examiner continues to take the disclosure of Yoshida out of context, in particular the statement "the use of a more specific and potent inhibitor of histone deacetylase...to carry out further more refined analysis;" (2) Yoshida solved the technical problem of finding a more specific and potent inhibitor by using the small molecule inhibitor of histone deacetylase referred to as (R0-Trichostatin A (TSA).

9. Additionally, Applicants argue that none of the cited references mention, either explicitly or implicitly, to look outside the small molecule art to design inhibitors of histone deacetylase. Applicants argue there is no motivation to combined the cited references, and furthermore argue that the combined teachings of the cited documents actually teach away from developing antisense inhibitors.

10. In response to applicant's argument that there is no suggestion, either explicitly or implicitly to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in art. (See 2143.01 [R-2] Suggestion or Motivation To Modify the References). In the instant case, the general knowledge of the art indicates that antisense provides a means to specifically inhibit the

expression of a target gene for the types of studies proposed by Yoshida et al., this art recognized knowledge is exemplified by the teachings of Taylor et al. and Bennett et al., cited above, for example.

Yoshida et al. clearly teach that there is a need to find a more potent and specific inhibitor of histone deacetylase for analysis of histone deacetylase activities. Yoshida et al. further discuss how the only other known histone deacetylase inhibitor, n-butyrate, has additional, multiple non-specific effects on cells. Yoshida et al. indicated that TSA appears to be a more specific inhibitor with fewer side effects than n-butyrate and therefore a useful tool for determining histone deacetylase activities in cells. The skilled artisan would clearly recognize the need to have other specific inhibitors of histone deacetylase as tools in elucidating the function of histone deacetylase, for example, to determine what TSA effects are, in fact, specific for histone deacetylase function, rather than non-specific TSA effects. Activity analysis for histone deacetylase, as taught and motivated by Yoshida et al., clearly would require multiple inhibitors as research tools, and as stated by Taylor et al. (page 562, 1st paragraph) "[a]ntisense oligonucleotides.....can be designed to inhibit any gene target provided that the sequence is known," and are "attractive candidates as therapeutic agents and as research tools for the elucidation of gene function."

Yoshida et al. do not suggest that TSA is the only specific inhibitor needed for this analysis, and further, Yoshida et al. point to the shortcomings of the only other known inhibitor and teach comparative analysis using both inhibitors to elucidate specific versus non-specific effects.

The skilled artisan would clearly recognize that other comparative experiments using other specific inhibitors would be useful and that antisense would fulfill that need, based on the teachings of the secondary references and would further recognize the advantages of the improved specificity provided by antisense over the small molecule inhibitors known in the art for HDAC-1. Antisense was a commonly known as an art accepted method of inhibition of a target gene in cells in cell culture and thus would have been an obvious choice for making a specific inhibitor of HDAC-1.

In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See In re Gorman, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Finally, Applicants provide multiple references published after the Yoshida et al. describing small molecule inhibitors, in particular TSA, of histone deacetylase to support his argument that there is no mention or suggestion of using antisense technology. Contrary to Applicant's assertions, although the reference cited by Applicants do not mention the use of antisense technology, antisense technology was well known at the time the instant invention was made as an attractive candidate for "research tools for the elucidation of gene function" of genes whose sequence was previously isolated (see GenBank Accession No. U50079). Applicant's arguments do not take the place of evidence to the contrary that the ordinary skilled artisan at the time of the instant invention would not have been motivated to combine the teachings of the cited references in the design of the instantly claimed invention.

11. Claims 1-3 and 5 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al. (IDS reference A3, IDS filed 10/09/01) in view of the collection of Taylor et al. (DDT VOI. 4, No. 12, 12/12/99, pages 562-567), Bennett et al. (Chapter 2, pages 13-46, from Methods in Molecular Medicine: Antisense Therapeutics, 1996), Page 5, Baracchini et al. (U.S. Patent 5,801,154) and Cowsert (U.S. Patent 5,951,455) and the sequence of HDAC-1 (instant SEQ ID NO: 2 from GenBank Accession No. U50079, Applicants own admission, page 9 of specification) for the same reasons of record set forth in the prior Official actions, and further in view of Schreiber et al.

The discussion of Yoshida et al., Taylor et al., Bennett et al., Baracchini et al., Cowsert, GenBank Accession No. U50079, and Applicant's admission on page 9 of the specification, as set forth in the prior Office Actions, is incorporated here. However, none of the above references explicitly disclose antisense oligonucleotides targeting histone deacetylase isoforms.

Schreiber et al. describe the design of antisense oligonucleotides of at least 12 nucleotides in length, that hybridizes under stringent conditions to at least 12 consecutive nucleotides of SEQ ID NO: 1-4 of Schreiber et al. SEQ ID NO: 1 of this reference encodes a histone deacetylase that comprises a sequence that is 99.4 % identical to nucleotides 111 through 1559 of SEQ ID NO: 2 of the instant application. Due to the high level of sequence similarity between the histone deacetylase gene (HD1) of Schreiber et al. and HDAC-1 (SEQ ID NO: 2) of the instant application, antisense oligonucleotides that are complementary to HD1 of the prior art, would necessarily be complementary to HDAC-1 of the instant application.

The antisense oligonucleotides of Schreiber et al. function to specifically hybridize under cellular conditions with cellular mRNA or genomic DNA encoding one or more of the histone

deacetylase genes so as to inhibit the expression of this gene by inhibiting transcription or translation (see page 5, lines 8-28). The antisense oligonucleotides are preferably modified oligonucleotides which are resistant to endogenous nucleases, and comprise for example phosphoramidate, phosphorothioate and methylphosphonate analogs of DNA or peptide nucleic acids (see page 27, lines 25-35).

One of ordinary skill in the art at the time of the instant invention would have been motivated to modify the teachings of the cited references to design the compounds of the instant invention since Schreiber et al. explicitly describe antisense oligonucleotides of at least 12 nucleotides in length which comprises a sequence that is complementary to a region of RNA or dsDNA that encodes a portion of HDAC-1, and are disclosed to function at least one of the histone deacetylase isoforms disclosed in Schreiber et al.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Schreiber et al. (WO 97/35990 A2).

Schreiber et al. describe the design of antisense oligonucleotides of at least 12 nucleotides in length, that hybridizes under stringent conditions to at least 12 consecutive nucleotides of SEQ ID NO: 1-4 of Schreiber et al. SEQ ID NO: 1 of this reference encodes a histone deacetylase that comprises a sequence that is 99.4 % identical to nucleotides 111 through 1559 of SEQ ID

NO: 2 of the instant application. Due to the high level of sequence similarity between the histone deacetylase gene (HD1) of Schreiber et al. and HDAC-1 (SEQ ID NO: 2) of the instant application, antisense oligonucleotides that are complementary to HD1 of the prior art, would necessarily be complementary to HDAC-1 of the instant application.

The antisense oligonucleotides of Schreiber et al. function to specifically hybridize under cellular conditions with cellular mRNA or genomic DNA encoding one or more of the histone deacetylase genes so as to inhibit the expression of this gene by inhibiting transcription or translation (see page 5, lines 8-28). The antisense oligonucleotides are preferably modified oligonucleotides, which are resistant to endogenous nucleases, and comprise for example phosphoramidate, phosphorothioate and methylphosphonate analogs of DNA or peptide nucleic acids (see page 27, lines 25-35).

Conclusion

14. Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 7 is considered free of the prior art since the prior art did not teach nor fairly suggest the sequences of instant SEQ ID NOS: 17 and 18.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571)272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Patent Examiner
Art Unit 1633

JLE